AWARD NUMBER: W81XWH-14-1-0476

TITLE: The Thoc1 Ribonucleoprotein as a Novel Biomarker for Prostate Cancer Treatment Assignment

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	15 Sep 2015 - 14 Sep 2016

4. TITLE AND SUBTITLE
The Thoc1 Ribonucleoprotein as a Novel Biomarker for Prostate Cancer Treatment Assignment

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0476

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
James L. Mohler, MD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
.
Health Research, Inc.
Buffalo, NY 14263

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Active surveillance (AS) is an option for men with low risk prostate cancer in order to reduce over treatment, but few men choose it because current prognostic indicators are imperfect. The objectives of this research are to test whether pThoc1 can improve the assignment of prostate cancer patients to therapy. We have made significant progress on the goals articulated in the Statement of Work. IRB/HRPO approval has been obtained for construction and use of new TMAs (PI Mohler and Goodrich). The TMAs from PCaP have been obtained (PI Mohler and Goodrich). Pathology analysis of 1146 patient specimens and construction of TMAs are completed and the TMA sections were requested, pending immunostaining(PI Mohler). Optimization of TMA staining is complete and staining of PCaP TMAs initiated (PI Goodrich). IRB/HRPO approval for active surveillance specimens has been obtained (PI Mohler, Goodrich).The PCaP Dx biopsy tissue sections were obtained for patients that would have qualified for active surveillance and they were immunostained (PI Mohler and Goodrich). Half of the RPCI Dx biopsies from active surveillance patients were pathology reviewed and obtained (PI Mohler). ELISA assays for measuring pThoc1 and pThoc1 autoantibodies have been successfully developed (PI Goodrich). Analysis of serum samples from a mouse model of prostate cancer has been performed, establishing feasibility (PI Goodrich). IRB/HRPO approval for serum samples has been obtained (PI Mohler, Goodrich). All preparative, optimization, and regulatory approval work has thus been completed, setting the stage for data gathering in year 2 of the grant. Over treatment is complicates the clinical management of prostate cancer. Improving the ability to distinguish aggressive from indolent disease is recognized as an unmet need by the 2013 PCRP Overarching Challenges. Identifying pThoc1 as a biomarker that can help meet this need will have significant impact.

15. SUBJECT TERMS
Prostate cancer, biomarker, active surveillance, prognostic indicator, tissue microarray, immunostaining, ribonucleoprotein

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	18	19b. TELEPHONE NUMBER *(include area code)*

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1. Introduction

Active surveillance (AS) has been proposed as an option for men with low risk prostate cancer in order to reduce over treatment. Only a fraction of eligible men choose AS, however, because current prognostic indicators are imperfect. Biomarkers that improve upon PSA levels, clinical stage and Gleason score to distinguish between prostate cancers that can be observed safely from those that require immediate treatment could help "right size" recommended treatment. The objectives of this proposal are to test whether pThoc1 can improve the assignment of prostate cancer patients to therapy, to test whether pThoc1 correlates with observed racial disparities in prostate cancer mortality, to determine whether pThoc1 can identify active surveillance patients whose prostate cancer will progress, and to develop methods to quantitate pThoc1 or pThoc1 autoantibody in serum. The general study design is to assay pThoc1 in independent cohorts of clinically annotated prostate cancer biospecimens for which clinical and follow up data is available using previously developed antibody reagents and immunostaining methods. Over treatment is a critical issue complicating the clinical management of prostate cancer. Improving the ability to distinguish aggressive from indolent disease in men newly diagnosed with prostate cancer is recognized as an unmet need by the 2013 PCRP Overarching Challenges. Identifying pThoc1 as a biomarker that can help meet this need will have significant impact.

2. Keywords

Prostate cancer, biomarker, active surveillance, prognostic indicator, tissue microarray, immunostaining, ribonucleoprotein

3. Accomplishments

The Years 1 and 2 Tasks for the Mohler laboratory were copied from the Statement of Work and progress reported for each bullet under each task for each specific aim.

Specific Aim 1) Characterize pThoc1 levels in independent cohorts of human prostate cancer radical prostatectomy specimens.

Task 1- Construct prostate TMAs

- Finish construction of 1146 patient TMAs

A team of four pathologists completed the review of the H&E stained tissue sections from each of the 1146 patients. 828 patients tissues were used for TMA construction. Construction of the new RPCI tissue microarray (TMA) set was completed and consists of 44 individual TMA blocks (Figure 1).

Figure 1. PrCa30-73 TMA blocks

TMA	Description	No. Patients
RPCI_PrCa30_	Prostatic adenocarcinoma cases that qualified to TCGA. Tumor and normal cores. Cases from 2007-2009.	20
RPCI_PrCa31_	Prostatic adenocarcinomacases that qualified to TCGA. Tumor and normal cores. Cases from 2009-2013.	22
RPCI_PrCa32_	African American prostatic adenocarcinoma cases not included in PrCa18. Tumor and normal cores. Cases from 2007-2012.	26
RPCI_PrCa33_	Prostatic adenocarcinoma cases from patients with biochemical persistence/recurrence. Tumor and normal cores. Cases from 2006-2007.	31
RPCI_PrCa34_	Prostatic adenocarcinoma cases from patients with biochemical persistence/recurrence. Tumor and normal cores. Cases from 2007-2008.	31
RPCI_PrCa35_	Prostatic adenocarcinoma cases from patients with biochemical persistence/recurrence. Tumor and normal cores. Cases from 2008-2009.	31
RPCI_PrCa36_	Prostatic adenocarcinoma cases from patients with biochemical persistence/recurrence. Tumor and normal cores. Cases from 2009-2010.	31
RPCI_PrCa37_	Prostatic adenocarcinoma cases from patients with biochemical persistence/recurrence. Tumor and normal cores. Cases from 2010-2011.	31
RPCI_PrCa38_	Prostatic adenocarcinoma cases from patients with biochemical persistence/recurrence. Tumor and normal cores. Cases from 2011-2012.	20
RPCI_PrCa39_	Prostatic adenocarcinoma cases from patients with biochemical persistence/recurrence. Tumor and normal cores. Cases from 2006-2012.	19
RPCI_PrCa40_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 6.Tumor and normal cores. Cases from 2005-2007.	31
RPCI_PrCa41_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 6.Tumor and normal cores. Cases from 2007-2008.	31
RPCI_PrCa42_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 6.Tumor and normal cores. Cases from 2008-2010.	31

RPCI_PrCa43_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 6.Tumor and normal cores. Cases from 2010-2012.	28
RPCI_PrCa44_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 6.Tumor and normal cores. Cases from 2006-2012.	24
RPCI_PrCa45_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 6.Tumor and normal cores. Cases from 2005-2011.	29
RPCI_PrCa46_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 8, 9, or 10.Tumor and normal cores. Cases from 2006-2009.	31
RPCI_PrCa47_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 8, 9, or 10.Tumor and normal cores. Cases from 2009-2011.	21
RPCI_PrCa48_	Extremes of grade cohort. Prostatic adenocarcinoma cases from patients with a gleason score of 8, 9, or 10.Tumor and normal cores. Cases from 2006-2012.	23
RPCI_PrCa49_	Extent of disease cohort; category 1 (worst). Prostatic adenocarcinoma cases from patients with LN/seminal vesicle invaded (margin irrelevant) status. Tumor and normal cores. Cases from 2006-2009.	31
RPCI_PrCa50_	Extent of disease cohort; category 1 (worst). Prostatic adenocarcinoma cases from patients with LN/seminal vesicle invaded (margin irrelevant)status. Tumor and normal cores. Cases from 2009-2011.	20
RPCI_PrCa51_	Extent of disease cohort; category 1 (worst). Prostatic adenocarcinoma cases from patients with LN/seminal vesicle invaded (margin irrelevant) status. Tumor and normal cores. Cases from 2007-2012.	19
RPCI_PrCa52_	Extent of disease cohort; category 2. Prostatic adenocarcinoma cases from patients with Margin positive, LN/seminal vesicle negative status. Tumor and normal cores. Cases from 2006-2007.	31
RPCI_PrCa53_	Extent of disease cohort; category 2. Prostatic adenocarcinoma cases from patients with Margin positive, LN/seminal vesicle negative status. Tumor and normal cores. Cases from 2007-2009.	31

RPCI_PrCa54_	Extent of disease cohort; category 2. Prostatic adenocarcinoma cases from patients with Margin positive, LN/seminal vesicle negative status. Tumor and normal cores. Cases from 2009-2010.	31
RPCI_PrCa55_	Extent of disease cohort; category 2. Prostatic adenocarcinoma cases from patients with Margin positive, LN/seminal vesicle negative status. Tumor and normal cores. Cases from 2010-2011.	31
RPCI_PrCa56_	Extent of disease cohort; category 2. Prostatic adenocarcinoma cases from patients with Margin positive, LN/seminal vesicle negative status. Tumor and normal cores. Cases from 2011-2012.	23
RPCI_PrCa57_	Extent of disease cohort; category 2. Prostatic adenocarcinoma cases from patients with Margin positive, LN/seminal vesicle negative status. Tumor and normal cores. Cases from 2007-2012.	23
RPCI_PrCa58_	Extent of disease cohort; category 3. Prostatic adenocarcinoma cases from patients with bladder neck invasion/extra-capsular extension, margin negative status. Tumor and normal cores. Cases from 2005-2007.	31
RPCI_PrCa59_	Extent of disease cohort; category 3. Prostatic adenocarcinoma cases from patients with bladder neck invasion/extra-capsular extension, margin negative status. Tumor and normal cores. Cases from 2007-2009.	31
RPCI_PrCa60_	Extent of disease cohort; category 3. Prostatic adenocarcinoma cases from patients with bladder neck invasion/extra-capsular extension, margin negative status. Tumor and normal cores. Cases from 2009-2011.	31
RPCI_PrCa61_	Extent of disease cohort; category 3. Prostatic adenocarcinoma cases from patients with bladder neck invasion/extra-capsular extension, margin negative status. Tumor and normal cores. Cases from 2011-2012.	22
RPCI_PrCa62_	Extent of disease cohort; category 3. Prostatic adenocarcinoma cases from patients with bladder neck invasion/extra-capsular extension, margin negative status. Tumor and normal cores. Cases from 2006-2012.	21

RPCI_PrCa63_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2006.	31
RPCI_PrCa64_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2006-2007.	31
RPCI_PrCa65_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2007.	31
RPCI_PrCa66_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2007-2008.	31
RPCI_PrCa67_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2008-2009.	31
RPCI_PrCa68_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2009-2010.	31
RPCI_PrCa69_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2010-2012.	31
RPCI_PrCa70_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2005-2012.	31
RPCI_PrCa71_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2006-2012.	22
RPCI_PrCa72_	Extent of disease cohort; category 4 (best). Prostatic adenocarcinoma cases from patients with organ confined, margin negative status. Tumor and normal cores. Cases from 2005-2012.	21

RPCI_PrCa73_	Prostatic adenocarcinoma; cases that did not fit any of the criteria to be included in TMAs PrCa30-PrCa72. Tumor and normal cores. Cases from 2010-2012.	21

- Obtain 328 AA and 361 CA patient TMAs from PCaP

The protocol was reviewed and approved by the North Carolina – Louisiana Prostate Cancer Project (PCaP) Management Committee. Their approval was contingent on successful development of the ELISA assay to detect Thoc1 and Thoc1 autoantibodies in serum samples. PCaP tissue sections were released October 2, 2015 since Dr. Goodrich's laboratory completed the feasibility study and submitted the supporting documentation.

- Obtain HRPO approval, amend IRB protocol

The protocol for this study was amended and reviewed and approved by the RPCI Genito-Urinary Disease Site Research Group (GU DSRG) and by the Office of Research Subject Protection (ORSP). The approval process took approximately 6 months. DoD PCRP approval required an additional 9 months when questioned the PCaP and RPCI granted exemption.

Task 2- Immunostain TMAs

- Further optimization of immunostaining

The immunohistochemistry methods have been optimized for immunostaining of Thoc1 and PMP22

- Immunostain RPCI 92 AA and 92 CA patient TMAs
- Immunostain 328 AA and 361 CA patient TMAs
- Immunostain 1146 patient TMAs

Immunostaing of the PCaP TMAs was completed. Immunostaining of the RPCI 92 AA and 92 CA and PrCa 30-73 TMA sets is underway.

Task 3- Analyze data

- Score pathology and immunostaining of TMA slides

Scoring of the acquired images, in collaboration with Dr. Azabdaftari is in progress.

- Correlate immunostaining with clinical data

Clinical data will be requested from the RPCI Prostate Database, when scoring is complete (to avoid bias).

Specific Aim 2) Characterize pThoc1 levels in a cohort of human prostate cancer patients on active surveillance.

Task 1- Immunostain active surveillance patient biopsies

- IRB/HRPO approval for active surveillance specimens

The protocol for this study was amended and reviewed and approved by the RPCI Genito-Urinary

Disease Site Research Group (GU DSRG) and by the Office of Research Subject Protection (ORSP). The approval process took approximately 6 months. DoD PCRP approval required an additional 9 months when questioned the PCaP and RPCI granted exemption.

Task 2- Enroll ~50 prostate cancer patients per year on active surveillance

- Annotate clinical data

Patients continue to be recommended and select active surveillance at RPCI. Each has all demographic, clinical, pathological and oncological outcome data entered prospectively in a relational database by our clinical team and data managers [435 are enrolled as of February 5, 2016, the date of this revised progress report].

- Immunostain biopsy tissue sections

385 patients are enrolled on active surveillance at RPCI [as of October 14,2015, the date of the original progress report]. Diagnostic prostate biopsy tissue specimens are available for only 53 patients. All other patients had prostate biopsies performed at other facilities. Obtaining them from individual pathology laboratories would be costly and time consuming, based on previous PCaP experience. The study group will be expanded by including diagnostic biopsy tissue sections from RPCI and PCaP patients who would have qualified for active surveillance (NCCN very low, low or favorable intermediate [T1c, Gleason grade 3+4, PSA < 10] prostate cancer). Approximately 250 research subject meet these criteria and could have prostate biopsy sections available for study.

DSRG and ORSP approvals were obtained at RPCI and from the PCaP Management Committee. The approval process took approximately 6 months. DoD PCRP approval required an additional 9 months when questioned the PCaP and RPCI granted exemption.

PCaP provided diagnostic prostate biopsies from 183 men October 2, 2015, which have been immunostained and visual scoring has begun. The RPCI diagnostic biopsy tissue sections are being prepared by the RPCI Pathology Resource Network (PRN) PRN has identified 100 cases that are enrolled on active surveillance at RPCI or they would have qualified for active surveillance, per NCCN guidlenies, but received a different treatment. 50 cases were reviewed by Dr. Azabdaftari and the remaining 50 cases are in process of review. Immunostaing will be completed as soon as the pathology review is completed.

Specific Aim 3) Test whether pThoc1 or autoantibodies against pThoc1 can be detected in the serum of prostate cancer patients.

Task 2- Assay serum pThoc1 or pThoc1 autoantibodies in human prostate cancer serum samples

- IRB/HRPO approval for serum samples

The protocol for this study was amended and reviewed and approved by the RPCI Genito-Urinary Disease Site Research Group (GU DSRG) and by the Office of Research Subject Protection (ORSP). The approval process took approximately 6 months. DoD PCRP approval required an additional 9 months when questioned the PCaP and RPCI granted exemption.

In summary, we are on schedule in all areas except RPCI TMA construction tooklonger than anticipated. All blocks have been selected and the TMA set designed and constructed.

- Methods adaptation to human samples if necessary

The serum pThoc1 and pThoc1 autoantibodies assay was standardized previously for mouse serum. Preliminary experiments using human serum showed that the assay required optimization, which should be completed before the end of 2016.

- Assay serum pThoc1 concentrations in RPCI serum samples
- Assay serum pThoc1 autoantibody titers in RPCI serum samples
- Assay serum pThoc1 concentrations in PCaP serum samples
- Assay serum pThoc1 autoantibody titers in PCaP serum samples

Sample analysis will be completed after the assay has been optimized.

4. Impact

None

5. Changes/Problems

None

6. Products

None

7. Participants & Other Collaborating Organizations

James L. Mohler, MD	Partnering PI	1 calendar months
Gissou Azabdaftari, MD	Co-Investigator	<1 calendar months
Elena Pop, MD	Co-Investigator	1 calendar months
Kristopher Attwood, PhD	Biostatistician	<1 calendar months
John Stocking	Lab technician	6 calendar months

No other organizations are involved in the research.

Changes in Other Support

James L. Mohler, MD

No Cost Extension
Title: Diet changes among prostate cancer patients under expectant management (Marshall - PI)
Time Commitments: 0.60 calendar months
Supporting Agency: National Cancer Institute
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Program Official: Howard L. Parnes, Email: hp24c@nih.gov Phone: 301-594-0920 Fax: 301-435-1564

Performance Period: 09/28/2009-**01/31/2017 (NCE)**
Level of Funding: $55,818
Brief description of project's goals: The focus of this study is to assess whether a diet emphasizing plant consumption decreases the probability that low grade, low-volume prostate cancer (LGLV)in expectant management(EM)patients progresses to a more aggressive form of cancer that merits active treatment. The intervention will be conducted through one of the leading cooperative oncology research groups: Cancer and Leukemia Group B (CALGB).
List of specific aims:
1. Assess the effect of a telephone-based dietary intervention on PSA, PSA doubling time, Gleason score and tumor extension in LGLV prostate cancer patients treated with EM.
2. Assess the effect of a telephone-based dietary intervention on treatment seeking, anxiety and coronary heart disease in prostate cancer patients treated with EM.

No Cost Extension
Title: Defining intra- and intertumoral genomic heterogeneity in prostate cancer (Mohler - PI)
Time Commitments: 0.60 calendar months
Supporting Agency: Roswell Park Alliance Foundation
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org
Performance Period: 12/10/2013-**12/31/2016 (NCE)**
Level of funding: $92,384
Brief description of project's goals:
Intra- and inter-tumoral CaP genomic heterogeneity necessitates extensive sampling of a radical prostatectomy specimen.
List of specific aims:
1. Determine intra- and inter-tumoral heterogeneity in CaP's mutational landscape using whole exome sequencing to determine heterogeneity within and among CaP foci derived from radical prostatectomy specimens from patients with high-risk disease who are expected to develop metastatic disease and require ADT
2. Define intra- and inter-tumoral CaP heterogeneity in structural gene rearrangement and gene expression patterns using RNA-Seq and RNA derived from the same CaP samples used in Aim 1

No Cost Extension
Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu – PI)
Time Commitments: 0.12 calendar months
Supporting Agency: NIH/NCI 1R21CA191895-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-276-5157, viviana.knowles@nih.gov
Performance Period: 09/17/2014-**08/31/2017 (NCE)**
Level of Funding: $419,884
Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.
List of specific aims:
1. Characterize the expression of STS and potential STS regulators in CRPC
2. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth
3. Identify DHEAS uptake mechanisms

No Cost Extension
Title: Cholesterol Lowering Intervention for Prostate Cancer Active Surveillance/Jr. Faculty Award to Alliance NCORP Research Base – Pilot Project (Kim/Mohler - PIs)
Time Commitments: 0.60 calendar months
Supporting Agency: Cedars/NCI
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Subcontract with Cedars Sinai. Cedars-Sinai Medical Center, Attention: Margaret Jenkins, Administrative Program Coordinator
Department of Surgery, Research Division, 8635 W. 3rd Street, Suite 973W, Los Angeles, CA 90048

margaret.jenkins@cshs.org
Performance Period: 04/01/2015 – **03/31/2017 (NCE)**
Level of funding: $93,955 (sub contract)
Brief description of project's goals: The proposed research tests the hypothesis that intensive cholesterol lowering will decrease the growth rate of benign and malignant prostate epithelium. The proposed research could provide the data necessary to justify a phase III clinical trial to address one of the major problems in urologic oncology how to prevent the progression of low risk prostate cancer to provide men higher levels of confidence for selection of active surveillance.

Prior pending, now active funding
Title: A Small-Molecule Inhibitor of the Terminal Steps for Intracrine Androgen Synthesis in Advanced Prostate Cancer (Mohler)
Time Commitments: .975 calendar months
Supporting Agency: NCI-1R21CA205108-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Nicole Franklin, Grants Management Specialist, National Cancer Institute, 9609 Medical Center Drive, West Tower, Room 2W556, Bethesda, MD 20892 (regular mail), Phone: 240-276-5210, Email: nicole.franklin@nih.gov
Performance Period: **04/10/2016-04/09/2018**
Level of Funding: $ 416,398
Brief description of project's goals: This research seeks to explore if a small-molecule inhibitor of the catalytic site shared by the five 3α−oxidoreductases will decrease T and DHT metabolism through the frontdoor and backdoor pathways.
List of specific aims:
1. Identify a candidate inhibitor against the catalytic site shared by the five 3α−oxidoreductases
2. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3α−oxidoreductases
3. Determine whether the inhibitor of the 3α−oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth

Prior pending, now active funding
Title: Understanding the Relative Contributions of and Critical Enzymes for the 3 Pathways for Intracrine Metabolism of Testicular Androgens in Advanced Prostate Cancer.
Time Commitments: 1.65 calendar months
Supporting Agency: DoD PC150326
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Tom Winter
Grants Specialist, Assistance Agreements Branch 4 U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702 Cell 240-357-1590 Office 301-619-2665 Thomas.s.winter2.civ@mail.mil
Performance Period: **09/30/2016-09/29/2019**
Level of funding: $660,315
Brief description of project's goals: This research seeks better understanding of intracrine androgen metabolism during ADT will identify new targets to reduce T and DHT production.
List of specific aims:
1. Determine the relative use of the 3 pathways for intracrine androgen metabolism in vitro, in vivo and in clinical specimens
2. Identify the principal androgen metabolism enzymes (i.e., 3α-oxidoreductases) responsible for primary backdoor DHT synthesis from androstanediol
3. Determine the requirements for SRD5A1-3 in the frontdoor pathway of DHT synthesis from T and its precursors and of SRD5A1 and HSD17B3 in the secondary backdoor pathway of DHT synthesis from androstenedione

Prior pending, now active funding
Title: The NF-kappaB-androgen Receptor Axis Drives Failure of Medical Therapy in Human Benign Prostatic Hyperplasia (Matusik)
Time Commitments: 0.30 calendar months
Supporting Agency: NIH/NIDDK Melissa Haney, Manager, Dept of Urologic Surgery, Vanderbilt University. 615-322-3172, Melissa.haney@vanderbilt.edu

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: not assigned
Performance Period: **09/16/2016 – 07/31/2021**
Level of funding: $151,840 (sub)
Brief description of project's goals: N□B and AR signaling controls the failed response to 5ARIs in BPH.
List of specific aims:
1. Determine cross-talk between NF□B and AR signaling to regulate failure of medical therapy
2. Determine the SRD5A isoforms contribution during resistance to medical therapy
3. Determine if failure of medical therapy is driven by NF□B and/or AR-V7 in BPH patients. New insight into how BPH patients fail 5α-reductase inhibitors holds the promise to identify pathways to apply novel approaches to medical therapy in the treatment of BPH.

Kristopher Attwood, PhD

Prior pending, now active funding
Title: Assessing the impact of differing pharmacy tobacco retail displays on smokers awareness, perceptions, and intentions to quit (1 R21 CA198824-01A1)
Time Commitments: 0.225 calendar (PI-Bansal Travers)
Supporting Agency: NIH
Grants Officer: Phone: Annette Kaufman; Annette.kaufman@nih.gov; (240) 276-6706
Performance Period: **6/1/16-5/31/18**
Level of Funding: $471,625
Brief description of project's goals: The goal of this timely project is to take advantage of the ongoing natural experiment in the three largest U.S. pharmacy chains to better understand consumer perceptions of differences in point-of-sale advertising for using and quitting tobacco, particularly how it is received, understood, and acted on by young adult cigarette smokers.
List of specific aims:
1. To determine consumer attention to current point-of-sale retail displays, the factors associated with different amounts and areas of attention, and whether attention to these displays influences consumer perceptions of the appeal and perceived relative risks of smoking cigarettes.
2. To determine consumer attention to current smoking cessation messages at point-of-sale retail displays, the factors associated with different amounts and areas of attention, and whether attention to these displays influences consumer perceptions of the perceived benefits of quitting.
3. To determine changes in quit intentions as a function of differences between pharmacy PoS retail displays.
4. To determine if consumer attention to cessation messages at the point-of-sale are associated with changes in intention to quit smoking.

Prior pending, now active funding
Title: Targeting ß-Adrenergic Signaling to Control GVH and GVL Responses (1 R21 CA202358-01A1)
Time Commitments: 0.30 calendar (PI-Cao)
Supporting Agency: NCI
Grants Officer: Karen Waddel Muszynski; Karen.muszynski2@nih.gov; Phone: (301) 846-1101
Performance Period: **07/15/16-06/30/18**
Level of Funding: $490,280
Brief description of project's goals: Based on our recently published work, the goal of this study is to explore a new paradigm regarding β2-AR mediated stress response during alloHCT. Using established murine models, we have discovered that pharmacologic or physiologic manipulation of β2-AR signaling exhibits a significant impact on the outcome of alloHCT.
List of specific aims:
1) Aim 1 will examine norepinephrine blood levels and ßAR blocker or agonist usage in HCT patients as potential factors influencing clinical outcomes.
a. We propose to measure norepinephrine plasma levels and examine ßAR blocker or agonist usage in about 200 de-identified allogeneic HCT patients, and define the relationship between ßAR stress signaling and its manipulation to clinical outcomes including GVHD incidence and severity, cancer relapse, and infection.
2) Aim 2 will evaluate the therapeutic potential of manipulating ßAR signaling to modulate GVH and GVT responses.

a. We have recently established a xenotransplantation system using humanized NSG mice as hosts to examine the GVH and GVT functions of human immune cells. We will use this new translational platform to evaluate the impact of manipulating ßAR-mediated signaling on GVT effect in the context of GVHD, and test the hypothesis that strategic application of agonists/antagonists to ßAR-mediated signaling can minimize GVHD while preserving or even enhancing the desired GVT effect.

3) Aim 3 will study the cellular mechanisms by which ßAR-mediated stress signaling impacts GVH and GVT responses.

a. This aim will be critical for our appreciation of how much ßAR-dependent signaling shapes the commonly accepted outcomes of GVHD and GVT effect in important pre-clinical models. We will use ßAR deficient mice to determine how ßAR signaling affects the functions of critical immune cell subsets known to dictate the onset and severity of GVHD and to mediate the favorable GVT effect. We will examine both donor-derived T cells and myeloid cells and host-type hematopoietic and non-hematopoietic cells.

Prior pending, now active funding
Title: Novel Mouse Models to Define Genetic Drivers of Aggressive Prostate Cancer (1R21 CA205627-01)
Time Commitments: 0.225 calendar (PI-Ellis)
Supporting Agency: NIH
Grants Officer: Grace Ault; grace.alt@nih.gov; Phone: (240) 276-6201
Performance Period: **04/15/16-03/31/18**
Level of Funding: $471,625
Brief description of project's goals: Our principle objective is to characterize our genetically engineered mouse models to discover genetic switches which drive aggressive prostate cancer. Overall, our proposed studies will significantly impact prostate cancer research and how patients are clinically assessed to determine stratification of indolent from aggressive disease.
List of specific aims:
1. Specifically, aim 1 will determine if the retinoblastoma protein (Rb) is a suppressor of PCa metastasis.
2. Specific aim 2 will utilize a sleeping beauty mutagenesis screen to identify novel candidate genetic drivers of PCa metastasis.

Prior pending, now active funding
Title: A Small-Molecule Inhibitor of the Terminal Steps for Intracrine Androgen Synthesis In Advanced Prostate Cancer (1 R21 CA205108-01)
Time Commitments: 0.30 calendar (PI-Mohler)
Supporting Agency: NIH
Grants Officer: Suresh Arya; suresh.arya@nih.gov; Phone: (240) 276-5906
Performance Period: **04/12/16-03/31/18**
Level of Funding: $489,524
Brief description of project's goals: The central hypothesis is that a small-molecule inhibitor of the catalytic site shared by the five 3a-oxidoreductases will decrease T and DHT metabolism through the frontdoor and backdoor pathways.
List of specific aims:
1. Identify a candidate inhibitor against the catalytic site shared by the five 3a-oxidoreductases.
2. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3a-oxidoreductases.
3. Determine whether the inhibitor of the 3a-oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth.

Prior pending, now active funding
Title: Leveraging the Methionine Salvage Pathway as a Novel Therapy for Prostate Cancer (1 R01 CA197996-01A1)
Time Commitments: 0.30 calendar (PI- Smiraglia)
Supporting Agency: NIH
Grants Officer: Elizabeth Woodhouse; Phone: (240) 276-6205; elizabeth.woodhouse@nih.gov
Performance Period: **05/01/2016-04/30/2021**
Level of Funding: $2,335,917

Brief description of project's goals: The objective of the current proposal is to determine the therapeutic potential of polyamine catabolism upregulation methylthioadenosine phosphor-ylase inhibition, either alone or in combination, to enhance the extent and/or duration of clinical benefit of androgen deprivation therapy. The central hypothesis is that the MSP is critical to CaP due to high metabolic flux through polyamine biosynthesis, and that this dependence can be enhanced by increasing the activity of spermidine/spermine N1-acetyltransferase.
List of specific aims:
1. To determine mechanisms of action and synergistic potential of MSP inhibition and activation of polyamine catabolism in cell line models.
2. To measure efficacy of MSP inhibition and/or activation of polyamine catabolism to treat established androgen independent CaP in human cell line xenografts.
3. To measure drug efficacy to prevent castration recurrence in human xenograft and mouse models of progression to ADT-RCaP.

Prior pending, now active funding
Title: Prostate Specific Androgen Transporters are the Missing Target for Complete ADT (1 R01 CA193829-01A1)
Time Commitments: 0.30 calendar (PI- Smith)
Supporting Agency: NIH
Grants Officer: Neeraja Sathyamoorthy; neeraja.sathyamoorthy@nih.gov; Phone: (240) 276-6220
Performance Period: **12/09/2015-11/30/2020**
Level of Funding: $2,193,750
Brief description of project's goals: This project will identify novel targets in prostate endothelial cells to provide a prostate-specific inhibition of uptake, metabolism and trans-cellular transport of the androgens from blood into the tissue, providing adjuvant therapies to make ADT durable/curative, minimize systemic side-effects, and improving therapeutic efficacy for use for treatment of organ-localized CaP.
List of specific aims:
1. Determine inter-patient variability in up-take and metabolism of circulating T and DHEA-S, expression profiles of genes associated with androgen uptake/metabolism in human pECs and CaP/pEpi cells, and the short-term effect of T-deprivation on these processes.
2. Define the molecular mechanisms that mediate uptake, trans-cellular transport and efflux of circulating androgens in human pECs and pEpi cells, and confirmed in pECs with CaP.
3. Determine whether interdiction of adrenal androgen usage by pEC and/or CaP/pEpi has the potential to enhance the effect of T-deprivation (ADT).

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No cost extension
Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu)
Time Commitments: 1.80 calendar months
Supporting Agency: NIH/NCI 1R21CA191895-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-276-5157, viviana.knowles@nih.gov
Performance Period: **09/17/2014-08/31/2017 (NCE)**
Level of Funding: $466,950
Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.
List of specific aims:
Aim 1. Characterize the expression of STS and potential STS regulators in CRPC
Aim 2. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth
Aim 3. Identify DHEAS uptake mechanisms

Prior pending, now active funding
Title: A Small-Molecule Inhibitor of the Terminal Steps for Intracrine Androgen Synthesis in Advanced Prostate Cancer (Mohler)
Time Commitments: 1.0 calendar months (year 2)

Supporting Agency: NCI-1R21CA205108-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Nicole Franklin, Grants Management Specialist, National Cancer Institute, 9609 Medical Center Drive, West Tower, Room 2W556, Bethesda, MD 20892 (regular mail), Phone: 240-276-5210, Email: nicole.franklin@nih.gov
Performance Period: **04/10/2016-04/09/2018**
Level of Funding: $ 416,398
Brief description of project's goals: This research seeks to explore if a small-molecule inhibitor of the catalytic site shared by the five 3α−oxidoreductases will decrease T and DHT metabolism through the frontdoor and backdoor pathways.
List of specific aims:
1. Identify a candidate inhibitor against the catalytic site shared by the five 3α−oxidoreductases
2. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3α−oxidoreductases
3. Determine whether the inhibitor of the 3α−oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth

Prior pending, now active funding
Title: Genetic and Epigenetic Prostate Cancer-Related Alterations in Early-Onset disease in African American Men (Woloszynska-Read)
Time Commitments: 0.60 calendar months
Supporting Agency: NYSDOH
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org
Performance Period: **11/01/2015-10/31/2017**
Level of Funding: $ 130,430
Brief description of project's goals: Determine the relative frequency of genetic lesions found in prostate cancer in tumors from African Americans and European Americans. Determine the relative frequency of genetic lesions found in prostate cancer in tumors from African Americans and European Americans.
List of specific aims:
1. To determine the relative frequency of common genetic lesions found in prostate cancer in tumors from African Americans and European Americans.
2. To determine potentially relevant transcriptomic and methylomic differences in tumors from African Americans and European Americans.

Prior pending, now active funding
Title: Understanding the Relative Contributions of and Critical Enzymes for the 3 Pathways for Intracrine Mebolism (Mohler)
Time Commitments: 0.90 calendar months
Supporting Agency: DoD Idea Development Award
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Tom Winter
Grants Specialist, Assistance Agreements Branch 4 U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702 Cell 240-357-1590 Office 301-619-2665 Thomas.s.winter2.civ@mail.mil
Performance Period: **09/30/2016 – 09/29/2019**
Level of funding: $660,315
Brief description of project's goals:
Better understanding of intracrine androgen metabolism during ADT will identify new targets to reduce T and DHT production.
List of specific aims:
1. Determine the relative use of the 3 pathways for intracrine androgen metabolism in vitro, in vivo and in clinical specimens.
2. Identify the principal androgen metabolism enzymes (ie. 3a-oxidoreductases) responsible for primary backdoor DHT synthesis from androstanediol.
3. Determine the requirements for SRD5A1-3 in the frontdoor pathway of DHT synthesis from T and its precursors and of SRD5A1 and HSD17B3 in the secondary backdoor pathway of DHT synthesis from androstanedione.

8. Special Reporting Requirements

This grant funds a Synergistic Idea Development Award in collaboration with Dr. David Goodrich (Partnering PI, Roswell Park Cancer Institute). Dr. Goodrich will be submitting an independent annual report describing his aspect of the work.